NDA 50-670/S-014
NDA 50-693/S-002
NDA 50-710/S-006
NDA 50-711/S-006
NDA 50-730/S-004
NDA 50-733/S-004

Pfizer Pharmaceuticals
Attention: Mr. Victor M. Clavelli
Director, Drug Regulatory Affairs
235 East 42nd Street
New York, NY 10017-5755

Dear Mr. Clavelli:

Please refer to your supplemental new drug applications dated September 15, 1999, received September 16, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zithromax® (azithromycin) Capsules, NDA 50-670; Zithromax® (azithromycin) Single Dose Packet, NDA 50-693; Zithromax® (azithromycin) Oral Suspension, NDA 50-7 10; Zithromax® (azithromycin) Tablets, NDA 50-711; Zithromax® (azithromycin) Tablets, NDA 50-730; and Zithromax® (azithromycin) for Injection NDA 50-733. We note that these applications are subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submission dated February 28,2000.

These "Changes Being Effected" supplemental new drug applications provide for the addition of adverse events based on reports from your Adverse Event Monitoring (AEM) system.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling (package insert submitted September 15, 1999). Accordingly, these supplemental applications are approved effective on the date of this letter.

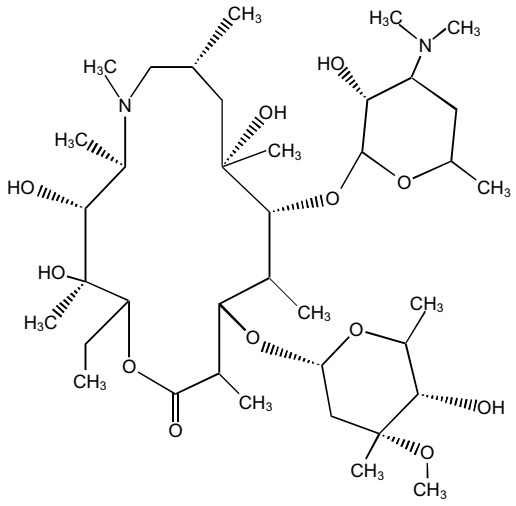
However, at the next printing of the labeling, we request that you delete "moniliasis" from ADVERSE REACTIONS, Post-Marketing Experience, Genitourinary and insert "oral candidiasis" under ADVERSE REACTIONS, Post-Marketing Experience, Gastrointestinal. In addition, ADVERSE REACTIONS, Post-Marketing Experience, Liver/Biliary should be changed to read as follows:
"Abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, some of which have resulted in death."

70-5179-00-7

ZITHROMAX®
(azithromycin tablets)
(azithromycin capsules)
and
(azithromycin for oral suspension)

DESCRIPTION

ZITHROMAX® (azithromycin tablets, azithromycin capsules and azithromycin for oral suspension) contain the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for oral administration. Azithromycin has the chemical name (*2R,3S,4R,5R,8R, 10R,11R,12S,13S,14R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-*L-ribo*-hexopyranosyl) oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-*D-xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is $C_{38}H_{72}N_2O_{12}$, and its molecular weight is 749.00. Azithromycin has the following structural formula:



Azithromycin, as the dihydrate, is a white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12}•2H_2O$ and a molecular weight of 785.0.

ZITHROMAX® is supplied for oral administration as film-coated, modified capsular shaped tablets containing azithromycin dihydrate equivalent to 250 mg azithromycin and the following inactive ingredients: dibasic calcium phosphate anhydrous, pregelatinized starch, sodium croscarmellose, magnesium stearate, sodium lauryl sulfate, hydroxypropyl methylcellulose, lactose, titanium dioxide, triacetin and D&C Red #30 aluminum lake.

ZITHROMAX® capsules contain azithromycin dihydrate equivalent to 250 mg of azithromycin. The capsules are supplied in red opaque hard-gelatin capsules (containing FD&C Red #40). They also contain the following inactive ingredients: anhydrous lactose, corn starch, magnesium stearate, and sodium lauryl sulfate.

It is also supplied as a powder for oral suspension.

ZITHROMAX® for oral suspension is supplied in bottles containing azithromycin dihydrate powder equivalent to 300 mg, 600 mg, 900 mg, or 1200 mg azithromycin per bottle and the following inactive ingredients: sucrose; sodium phosphate, tribasic, anhydrous; hydroxypropyl cellulose; xanthan gum; FD&C Red #40; and spray dried artificial cherry, creme de vanilla and banana flavors. After constitution, each 5 mL of suspension contains 100 mg or 200 mg of azithromycin.

CLINICAL PHARMACOLOGY

Adult Pharmacokinetics: Following oral administration, azithromycin is rapidly absorbed and widely distributed throughout the body. Rapid distribution of azithromycin into tissues and high concentration within cells result in significantly higher azithromycin concentrations in tissues than in plasma or serum.

The pharmacokinetic parameters of azithromycin capsules in plasma after a loading dose of 500 mg (2–250 mg capsules) on day one followed by 250 mg (1–250 mg capsule) q.d. on days two through five in healthy young adults (age 18-40 years old) are portrayed in the following chart:

Pharmacokinetic Parameters (Mean)	Total n=12	
	Day 1	Day 5
C_{max} (μg/mL)	0.41	0.24
T_{max} (h)	2.5	3.2
AUC_{0-24} (μg·h/mL)	2.6	2.1
C_{min} (μg/mL)	0.05	0.05
Urinary Excret. (% dose)	4.5	6.5

In this study, there was no significant difference in the disposition of azithromycin between male and female subjects. Plasma concentrations of azithromycin following single 500 mg oral and i.v. doses declined in a polyphasic pattern resulting in an average terminal half-life of 68 hours. With a regimen of 500 mg on Day 1 and 250 mg/day on Days 2-5, C_{min} and C_{max} remained essentially

unchanged from Day 2 through Day 5 of therapy. However, without a loading dose, azithromycin C_{min} levels required 5 to 7 days to reach steady-state.

In an open, randomized, two-way crossover study, pharmacokinetic parameters (AUC_{0-72}, C_{max}, T_{max}) determined from 36 fasted healthy male volunteers who received two 250-mg commercial capsules and two 250-mg tablets were:

	Capsule	Tablet	90% CI
AUC_{0-72} (μg·h/mL)	4.1 (1.2)	4.3 (1.2)	(99-113%)
C_{max} (μg/mL)	0.5 (0.2)	0.5 (0.2)	(96-121%)
T_{max} (hours)	2.1 (0.8)	2.2 (0.9)	

When azithromycin capsules were administered with food to 11 adult healthy male subjects, the rate of absorption (C_{max}) of azithromycin from the capsule formulation was reduced by 52% and the extent of absorption (AUC) by 43%.

In an open label, randomized, two-way crossover study in 12 healthy subjects to assess the effect of a high fat standard meal on the serum concentrations of azithromycin resulting from the oral administration of two 250-mg film-coated tablets, it was shown that food increased C_{max} by 23% while there was no change in AUC.

When azithromycin suspension was administered with food to 28 adult healthy male subjects, the rate of absorption (C_{max}) was increased by 56% while the extent of absorption (AUC) was unchanged.

The AUC of azithromycin was unaffected by co-administration of an antacid containing aluminum and magnesium hydroxide with ZITHROMAX® capsules (azithromycin); however, the C_{max} was reduced by 24%. Administration of cimetidine (800 mg) two hours prior to azithromycin had no effect on azithromycin absorption.

When studied in healthy elderly subjects from age 65 to 85 years, the pharmacokinetic parameters of azithromycin in elderly men were similar to those in young adults; however, in elderly women, although higher peak concentrations (increased by 30 to 50%) were observed, no significant accumulation occurred.

The high values in adults for apparent steady-state volume of distribution (31.1 L/kg) and plasma clearance (630 mL/min) suggest that the prolonged half-life is due to extensive uptake and subsequent release of drug from tissues.

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 μg/mL to 7% at 2 μg/mL.

Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

There are no pharmacokinetic data available from studies in hepatically- or renally-impaired individuals.

The effect of azithromycin on the plasma levels or pharmacokinetics of theophylline administered in multiple doses adequate to reach therapeutic steady-state plasma levels is not known. (See **PRECAUTIONS**.)

Selected tissue (or fluid) concentration and tissue (or fluid) to plasma/serum concentration ratios are shown in the following table:

AZITHROMYCIN CONCENTRATIONS FOLLOWING
TWO–250 mg (500 mg) CAPSULES IN ADULTS

TISSUE OR FLUID	TIME AFTER DOSE (h)	TISSUE OR FLUID CONCENTRATION (μg/g or μg/mL)[1]	CORRESPONDING PLASMA OR SERUM LEVEL (μg/mL)	TISSUE (FLUID) PLASMA (SERUM) RATIO[1]
SKIN	72-96	0.4	0.012	35
LUNG	72-96	4.0	0.012	>100
SPUTUM*	2-4	1.0	0.64	2
SPUTUM**	10-12	2.9	0.1	30
TONSIL***	9-18	4.5	0.03	>100
TONSIL***	180	0.9	0.006	>100
CERVIX****	19	2.8	0.04	70

[1] High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy. The antimicrobial activity of azithromycin is pH related. Azithromycin is concentrated in cell lysosomes which have a low intraorganelle pH, at which the drug's activity is reduced. However, the extensive distribution of drug to tissues may be relevant to clinical activity.

* Sample was obtained 2-4 hours after the first dose.

** Sample was obtained 10-12 hours after the first dose.

*** Dosing regimen of 2 doses of 250 mg each, separated by 12 hours.

**** Sample was obtained 19 hours after a single 500 mg dose.

The extensive tissue distribution was confirmed by examination of additional tissues and fluids (bone, ejaculum, prostate, ovary, uterus, salpinx, stomach, liver, and gallbladder). As there are no data from adequate and well-controlled studies of azithromycin treatment of infections in these additional body sites, the clinical significance of these tissue concentration data is unknown.

Following a regimen of 500 mg on the first day and 250 mg daily for 4 days, only very low concentrations were noted in cerebrospinal fluid (less than 0.01 μg/mL) in the presence of non-inflamed meninges.

Pediatric Pharmacokinetics:
In two clinical studies, azithromycin for oral suspension was dosed at 10 mg/kg on day 1, followed by 5 mg/kg on days 2 through 5 to two groups of children (aged 1-5 years and 5-15 years, respectively). The mean pharmacokinetic parameters at Day 5 were C_{max}=0.216 μg/mL, T_{max}=1.9 hours, and AUC_{0-24}=1.822 μg·hr/mL for the 1- to 5-year-old group and were C_{max}=0.383 μg/mL, T_{max}=2.4 hours, and AUC_{0-24}=3.109 μg·hr/mL for the 5- to 15-year-old group.

There are no pharmacokinetic data on azithromycin suspension when administered at a dose of 12 mg/kg/day in the presence or absence of food. (For the pediatric pharyngitis/tonsillitis dose, see **DOSAGE AND ADMINISTRATION.**)

Microbiology: Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected.

Azithromycin concentrates in phagocytes and fibroblasts as demonstrated by *in vitro* incubation techniques. Using such methodology, the ratio of intracellular to extracellular concentration was >30 after one hour incubation. *In vivo* studies suggest that concentration in phagocytes may contribute to drug distribution to inflamed tissues.

Azithromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms
Staphylococcus aureus
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

NOTE: Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains. Most strains of *Enterococcus faecalis* and methicillin-resistant staphylococci are resistant to azithromycin.

Aerobic gram-negative microorganisms
Haemophilus ducreyi
Haemophilus influenzae
Moraxella catarrhalis
Neisseria gonorrhoeae

"Other" microorganisms
Chlamydia pneumoniae
Chlamydia trachomatis
Mycoplasma pneumoniae

Beta-lactamase production should have no effect on azithromycin activity.

The following *in vitro* data are available, **but their clinical significance is unknown.**

Azithromycin exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 0.5 μg/mL or less against most (≥90%) strains of streptococci and MIC's of 2.0 μg/mL or less against most (≥90%) strains of other listed microorganisms. However, the safety and effectiveness of azithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic gram-positive microorganisms
Streptococci (Groups C, F, G)
Viridans group streptococci

Aerobic gram-negative microorganisms
Bordetella pertussis
Legionella pneumophila

Anaerobic microorganisms
Peptostreptococcus species
Prevotella bivia

"Other" microorganisms
Ureaplasma urealyticum

Susceptibility Tests
Azithromycin can be solubilized for *in vitro* susceptibility testing using dilution techniques by dissolving in a minimum amount of 95% ethanol and diluting to the working stock concentration with broth. Further dilutions may be made in water.

Dilution Techniques:
Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of azithromycin powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms other than *Haemophilus* species, *Neisseria gonorrhoeae*, and streptococci:

MIC (µg/mL)	Interpretation
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	Resistant (R)

For testing *Haemophilus* species:[a]

MIC (µg/mL)	Interpretation
≤ 4	Susceptible (S)

[a]These interpretive standards are applicable only to broth microdilution susceptibility testing with *Haemophilus* species using Haemophilus Test Medium.[1]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing Streptococci including *S. pneumoniae*:[b]

MIC (µg/mL)	Interpretation
≤ 0.5	Susceptible (S)
1	Intermediate (I)
≥ 2	Resistant (R)

[b]These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

No interpretive criteria have been established for testing *Neisseria gonorrhoeae.* This species is not usually tested.

A report of "Susceptible" indicates that the pathogen is likely to respond to monotherapy with azithromycin. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that achievable drug concentrations are unlikely to be inhibitory; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard azithromycin powder should provide the following MIC values:

Microorganism	MIC (µg/mL)
Haemophilus influenzae ATCC 49247[a]	1.0-4.0
Staphylococcus aureus ATCC 29213	0.5-2.0
Streptococcus pneumoniae ATCC 49619[b]	0.06-0.25

[a]This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using Haemophilus Test Medium (HTM).[1]

[b]This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

No interpretive criteria have been established for testing *Neisseria gonorrhoeae.* This species is not usually tested.

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15-µg azithromycin to test the susceptibility of microorganisms to azithromycin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15-µg azithromycin disk should be interpreted according to the following criteria:

For testing aerobic microorganisms (including streptococci)[a] except *Haemophilus* species and *Neisseria gonorrhoeae:*

Zone Diameter (mm)	Interpretation
≥ 18	Susceptible (S)
14-17	Intermediate (I)
≤ 13	Resistant (R)

[a]These zone diameter standards for streptococci apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

For testing *Haemophilus* species:[b]

Zone Diameter (mm)	Interpretation
≥ 12	Susceptible (S)

[b]These zone diameter standards apply only to tests with *Haemophilus* species using Haemophilus Test Medium (HTM).[2]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

No interpretive criteria have been established for testing *Neisseria gonorrhoeae.* This species is not usually tested.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for azithromycin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 15-µg azithromycin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
Haemophilus influenzae ATCC 49247[a]	13-21
Staphylococcus aureus ATCC 25923	21-26
Streptococcus pneumoniae ATCC 49619[b]	19-25

[a]These quality control limits apply only to tests conducted with *H. influenzae* ATCC 49247 using Haemophilus Test Medium (HTM).[2]

[b]These quality control limits apply only to tests conducted with *S. pneumoniae* ATCC 49619 using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

INDICATIONS AND USAGE

ZITHROMAX® (azithromycin) is indicated for the treatment of patients with mild to moderate infections (pneumonia: see **WARNINGS**) caused by susceptible strains of the designated microorganisms in the specific conditions listed below. As recommended dosages, durations of therapy, and applicable patient populations vary among these infections, please see **DOSAGE AND ADMINISTRATION** for specific dosing recommendations.

Adults:
Acute bacterial exacerbations of chronic obstructive pulmonary disease due to *Haemophilus influenzae, Moraxella catarrhalis*, or *Streptococcus pneumoniae*.

Community-acquired pneumonia due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae* in patients appropriate for oral therapy.

NOTE: Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following:

patients with cystic fibrosis,
patients with nosocomially acquired infections,
patients with known or suspected bacteremia,
patients requiring hospitalization,
elderly or debilitated patients, or
patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pharyngitis/tonsillitis caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy.

NOTE: Penicillin by the intramuscular route is the usual drug of choice in the treatment of *Streptococcus pyogenes* infection and the prophylaxis of rheumatic fever. ZITHROMAX® is often effective in the eradication of susceptible strains of *Streptococcus pyogenes* from the nasopharynx. Because some strains are resistant to ZITHROMAX®, susceptibility tests should be performed when patients are treated with ZITHROMAX®. Data establishing efficacy of azithromycin in subsequent prevention of rheumatic fever are not available.

Uncomplicated skin and skin structure infections due to *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Streptococcus agalactiae*. Abscesses usually require surgical drainage.

Urethritis and cervicitis due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.

Genital ulcer disease in men due to *Haemophilus ducreyi* (chancroid). Due to the small number of women included in clinical trials, the efficacy of azithromycin in the treatment of chancroid in women has not been established.

ZITHROMAX®, at the recommended dose, should not be relied upon to treat syphilis. Antimicrobial agents used in high doses for short periods of time to treat non-gonococcal urethritis may mask or delay the symptoms of incubating syphilis. All patients with sexually-transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate cultures for gonorrhea performed at the time of diagnosis. Appropriate antimicrobial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative organism and its susceptibility to azithromycin. Therapy with ZITHROMAX® may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.

Children: (See **Pediatric Use** and **CLINICAL STUDIES IN PEDIATRIC PATIENTS**.)

Acute otitis media caused by *Haemophilus influenzae*, *Moraxella catarrhalis,* or *Streptococcus pneumoniae*. (For specific dosage recommendation, see **DOSAGE AND ADMINISTRATION**.)

Community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae,* or *Streptococcus pneumoniae* in patients appropriate for oral therapy. (For specific dosage recommendation, see **DOSAGE AND ADMINISTRATION**.)

NOTE: Azithromycin should not be used in pediatric patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following:

patients with cystic fibrosis,
patients with nosocomially acquired infections,
patients with known or suspected bacteremia,
patients requiring hospitalization, or
patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pharyngitis/tonsillitis caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy. (For specific dosage recommendation, see **DOSAGE AND ADMINISTRATION**.)

NOTE: Penicillin by the intramuscular route is the usual drug of choice in the treatment of *Streptococcus pyogenes* infection and the prophylaxis of rheumatic fever. ZITHROMAX® is often effective in the eradication of susceptible strains of *Streptococcus pyogenes* from the nasopharynx. Because some strains are resistant to ZITHROMAX®, susceptibility tests should be performed when patients are treated with ZITHROMAX®. Data establishing efficacy of azithromycin in subsequent prevention of rheumatic fever are not available.

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative organism and its susceptibility to azithromycin. Therapy with ZITHROMAX® may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.

CONTRAINDICATIONS

ZITHROMAX® is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, or any macrolide antibiotic.

WARNINGS

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy. Although rare, fatalities have been reported. (See **CONTRAINDICATIONS**.) Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms **recurred soon thereafter in some patients without further azithromycin exposure**. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at present.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

In the treatment of pneumonia, azithromycin has only been shown to be safe and effective in the treatment of community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae,* or *Streptococcus pneumoniae* in patients appropriate for oral therapy. Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General: Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function. There are no data regarding azithromycin usage in patients with renal impairment; thus, caution should be exercised when prescribing azithromycin in these patients.

The following adverse events have not been reported in clinical trials with azithromycin, an azalide; however, they have been reported with macrolide products: ventricular arrhythmias, including ventricular tachycardia and *torsade de pointes*, in individuals with prolonged QT intervals.

There has been a spontaneous report from the post-marketing experience of a patient with previous history of arrhythmias who experienced *torsade de pointes* and subsequent myocardial infarction following a course of azithromycin therapy.

Information for Patients:
Patients should be cautioned to take ZITHROMAX® capsules and ZITHROMAX® suspension at least one hour prior to a meal or at least two hours after a meal. These medications should not be taken with food.

ZITHROMAX® tablets can be taken with or without food.

Patients should also be cautioned not to take aluminum- and magnesium-containing antacids and azithromycin simultaneously.

The patient should be directed to discontinue azithromycin immediately and contact a physician if any signs of an allergic reaction occur.

Drug Interactions: Aluminum- and magnesium-containing antacids reduce the peak serum levels (rate) but not the AUC (extent) of azithromycin absorption.

Administration of cimetidine (800 mg) two hours prior to azithromycin had no effect on azithromycin absorption.

Azithromycin did not affect the plasma levels or pharmacokinetics of theophylline administered as a single intravenous dose. The effect of azithromycin on the plasma levels or pharmacokinetics of theophylline administered in multiple doses resulting in therapeutic steady-state levels of theophylline is not known. However, concurrent use of macrolides and theophylline has been associated with increases in the serum concentrations of theophylline. Therefore, until further data are available, prudent medical practice dictates careful monitoring of plasma theophylline levels in patients receiving azithromycin and theophylline concomitantly.

Azithromycin did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

The following drug interactions have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. Nonetheless, they have been observed with macrolide products. Until further data are developed regarding drug interactions when azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised:

Digoxin–elevated digoxin levels.
Ergotamine or dihydroergotamine–acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.
Triazolam–decrease the clearance of triazolam and thus may increase the pharmacologic effect of triazolam.
Drugs metabolized by the cytochrome P^{450} system–elevations of serum carbamazepine, terfenadine, cyclosporine, hexobarbital, and phenytoin levels.

Laboratory Test Interactions: There are no reported laboratory test interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. No evidence of impaired fertility due to azithromycin was found.

Pregnancy: Teratogenic Effects. Pregnancy Category B: Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose levels (i.e., 200 mg/kg/day). These doses, based on a mg/m^2 basis, are estimated to be 4 and 2 times, respectively, the human daily dose of 500 mg. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether azithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when azithromycin is administered to a nursing woman.

Pediatric Use: (See **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE,** and **DOSAGE AND ADMINISTRATION**.)

Acute Otitis Media (dosage regimen: 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5): Safety and effectiveness in the treatment of children with otitis media under 6 months of age have not been established.

Community-Acquired Pneumonia (dosage regimen: 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5): Safety and effectiveness in the treatment of children with community-acquired pneumonia under 6 months of age have not been established. Safety and effectiveness for pneumonia due to *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* were documented in pediatric clinical trials. Safety and effectiveness for pneumonia due to *Haemophilus influenzae* and *Streptococcus pneumoniae* were not documented bacteriologically in the pediatric clinical trial due to difficulty in obtaining specimens. Use of azithromycin for these two microorganisms is supported, however, by evidence from adequate and well-controlled studies in adults.

Pharyngitis/Tonsillitis (dosage regimen: 12 mg/kg on Days 1-5): Safety and effectiveness in the treatment of children with pharyngitis/tonsillitis under 2 years of age have not been established.

Studies evaluating the use of repeated courses of therapy have not been conducted. (See CLINICAL PHARMACOLOGY and ANIMAL TOXICOLOGY.)

Geriatric Use: Pharmacokinetic parameters in older volunteers (65-85 years old) were similar to those in younger volunteers (18-40 years old) for the 5-day therapeutic regimen. Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen. (See **CLINICAL PHARMACOLOGY**.)

ADVERSE REACTIONS

In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Approximately 0.7% of the patients (adults and children) from the multiple-dose clinical trials discontinued ZITHROMAX® (azithromycin) therapy because of treatment-related side effects. Most of the side effects leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain. Potentially serious side effects of angioedema and cholestatic jaundice were reported rarely.

Clinical:
Adults:
Multiple-dose regimen: Overall, the most common side effects in adult patients receiving a multiple-dose regimen of ZITHROMAX® were related to the gastrointestinal system with

diarrhea/loose stools (5%), nausea (3%), and abdominal pain (3%) being the most frequently reported.

No other side effects occurred in patients on the multiple-dose regimen of ZITHROMAX® with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:

Cardiovascular: Palpitations, chest pain.
Gastrointestinal: Dyspepsia, flatulence, vomiting, melena, and cholestatic jaundice.
Genitourinary: Monilia, vaginitis, and nephritis.
Nervous System: Dizziness, headache, vertigo, and somnolence.
General: Fatigue.
Allergic: Rash, photosensitivity, and angioedema.

Single 1-gram dose regimen: Overall, the most common side effects in patients receiving a single-dose regimen of 1 gram of ZITHROMAX® were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.

Side effects that occurred in patients on the single one-gram dosing regimen of ZITHROMAX® with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%), and vaginitis (1%).

Single 2-gram dose regimen: Overall, the most common side effects in patients receiving a single 2-gram dose of ZITHROMAX® were related to the gastrointestinal system. Side effects that occurred in patients in this study with a frequency of 1% or greater included nausea (18%), diarrhea/loose stools (14%), vomiting (7%), abdominal pain (7%), vaginitis (2%), dyspepsia (1%), and dizziness (1%). The majority of these complaints were mild in nature.

Children:
Multiple-dose regimens: The types of side effects in children were comparable to those seen in adults, with different incidence rates for the two dosage regimens recommended in children.

Acute Otitis Media: For the recommended dosage regimen of 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5, the most frequent side effects attributed to treatment were diarrhea/loose stools (2%), abdominal pain (2%), vomiting (1%), and nausea (1%).

Community-Acquired Pneumonia: For the recommended dosage regimen of 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5, the most frequent side effects attributed to treatment were diarrhea/loose stools (5.8%), abdominal pain, vomiting, and nausea (1.9% each), and rash (1.6%).

Pharyngitis/tonsillitis: For the recommended dosage regimen of 12 mg/kg on Days 1-5, the most frequent side effects attributed to treatment were diarrhea/loose stools (6%), vomiting (5%), abdominal pain (3%), nausea (2%), and headache (1%).

With either treatment regimen, no other side effects occurred in children treated with ZITHROMAX® with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:

Cardiovascular: Chest pain.
Gastrointestinal: Dyspepsia, constipation, anorexia, flatulence, and gastritis.
Nervous System: Headache (otitis media dosage), hyperkinesia, dizziness, agitation, nervousness, insomnia.
General: Fever, fatigue, malaise.
Allergic: Rash.
Skin and Appendages: Pruritus, urticaria.
Special Senses: Conjunctivitis.

Post-Marketing Experience:
Adverse events reported with azithromycin during the post-marketing period in adult and/or pediatric patients for which a causal relationship may not be established include:

Allergic: Arthralgia, edema, urticaria, angioedema.
Cardiovascular: Arrhythmias including ventricular tachycardia.
Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea rarely resulting in dehydration, pseudomembranous colitis and rare reports of tongue discoloration.
General: Asthenia, paresthesia and anaphylaxis (rarely fatal).
Genitourinary: Interstitial nephritis and acute renal failure, moniliasis, vaginitis.
Hematopoietic: Thrombocytopenia.
Liver/Biliary: Abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, which have rarely resulted in death.
Nervous System: Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, and agitation.
Psychiatric: Aggressive reaction and anxiety.
Skin/Appendages: Pruritus, rarely serious skin reactions including erythema multiforme, Stevens Johnson Syndrome, and toxic epidermal necrolysis.
Special Senses: Hearing disturbances including hearing loss, deafness, and/or tinnitus, rare reports of taste perversion.

Laboratory Abnormalities:
Adults:
Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows: with an incidence of 1-2%, elevated serum creatine phosphokinase, potassium, ALT (SGPT), GGT, and AST (SGOT); with an incidence of less than 1%, leukopenia, neutropenia, decreased platelet count, elevated serum alkaline phosphatase, bilirubin, BUN, creatinine, blood glucose, LDH, and phosphate.

When follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose clinical trials involving more than 3000 patients, 3 patients discontinued therapy because of treatment-related liver enzyme abnormalities and 1 because of a renal function abnormality.

Children:
Significant abnormalities (irrespective of drug relationship) occurring during clinical trials were all reported at a frequency of less than 1%, but were similar in type to the adult pattern.

In multiple-dose clinical trials involving almost 3300 pediatric patients, no patients discontinued therapy because of treatment-related laboratory abnormalities.

DOSAGE AND ADMINISTRATION
(See INDICATIONS AND USAGE and CLINICAL PHARMACOLOGY.)

Adults:
The recommended dose of ZITHROMAX® for the treatment of mild to moderate acute bacterial exacerbations of chronic obstructive pulmonary disease, community-acquired pneumonia of mild severity, pharyngitis/tonsillitis (as second-line therapy), and uncomplicated skin and skin structure infections due to the indicated organisms is: 500 mg as a single dose on the first day followed by 250 mg once daily on days 2 through 5.

ZITHROMAX® capsules should be given at least 1 hour before or 2 hours after a meal. ZITHROMAX® capsules should not be taken with food.

ZITHROMAX® tablets can be taken with or without food.

The recommended dose of ZITHROMAX® for the treatment of genital ulcer disease due to *Haemophilus ducreyi* (chancroid), non-gonococcal urethritis and cervicitis due to *C. trachomatis* is: a single 1 gram (1000 mg) dose of ZITHROMAX®.

The recommended dose of ZITHROMAX® for the treatment of urethritis and cervicitis due to *Neisseria gonorrhoeae* is a single 2 gram (2000 mg) dose of ZITHROMAX®.

Children:
Acute Otitis Media and Community-Acquired Pneumonia: The recommended dose of ZITHROMAX® for oral suspension for the treatment of children with acute otitis media and community-acquired pneumonia is 10 mg/kg as a single dose on the first day (not to exceed 500 mg/day) followed by 5 mg/kg on days 2 through 5 (not to exceed 250 mg/day). (See chart below.)

ZITHROMAX® for oral suspension should be given at least 1 hour before or 2 hours after a meal.

ZITHROMAX® for oral suspension should not be taken with food.

PEDIATRIC DOSAGE GUIDELINES FOR OTITIS MEDIA AND COMMUNITY-ACQUIRED PNEUMONIA
(Age 6 months and above, see Pediatric Use.)
Based on Body Weight

OTITIS MEDIA AND COMMUNITY-ACQUIRED PNEUMONIA

Dosing Calculated on 10 mg/kg on Day 1 dose, followed by 5 mg/kg on Days 2 to 5.

Weight		100 mg/5 mL Suspension		200 mg/5 mL Suspension		
Kg	lbs	Day 1	Days 2-5	Day 1	Days 2-5	Total mL per Treatment Course
10	22	5 mL (1 tsp)	2.5 mL (½ tsp)			15 mL
20	44			5 mL (1 tsp)	2.5 mL (½ tsp)	15 mL
30	66			7.5 mL (1½ tsp)	3.75 mL (¾ tsp)	22.5 mL
40	88			10 mL (2 tsp)	5 mL (1 tsp)	30 mL

Pharyngitis/Tonsillitis: The recommended dose for children with pharyngitis/tonsillitis is 12 mg/kg once a day for 5 days (not to exceed 500 mg/day). (See chart below.)

ZITHROMAX® for oral suspension should be given at least 1 hour before or 2 hours after a meal.

ZITHROMAX® for oral suspension should not be taken with food.

PEDIATRIC DOSAGE GUIDELINES FOR PHARYNGITIS/TONSILLITIS
(Age 2 years and above, see Pediatric Use.)
Based on Body Weight

PHARYNGITIS/TONSILLITIS

Dosing Calculated on 12 mg/kg once daily Days 1 to 5.

Weight		200 mg/5 mL Suspension	
Kg	lbs	Day 1-5	Total mL per Treatment Course
8	18	2.5 mL (½ tsp)	12.5 mL
17	37	5 mL (1 tsp)	25 mL
25	55	7.5 mL (1½ tsp)	37.5 mL
33	73	10 mL (2 tsp)	50 mL
40	88	12.5 mL (2½ tsp)	62.5 mL

Constituting instructions for ZITHROMAX® Oral Suspension, 300, 600, 900, 1200 mg bottles. The table below indicates the volume of water to be used for constitution:

Amount of water to be added	Total volume after constitution (azithromycin content)	Azithromycin concentration after constitution
9 mL (300 mg)	15 mL (300 mg)	100 mg/5 mL
9 mL (600 mg)	15 mL (600 mg)	200 mg/5 mL
12 mL (900 mg)	22.5 mL (900 mg)	200 mg/5 mL
15 mL (1200 mg)	30 mL (1200 mg)	200 mg/5 mL

Shake well before each use. Oversized bottle provides shake space. Keep tightly closed.

After mixing, store at 5° to 30°C (41° to 86°F) and use within 10 days. Discard after full dosing is completed.

HOW SUPPLIED

ZITHROMAX® tablets are supplied as red modified capsular shaped, engraved, film-coated tablets containing azithromycin dihydrate equivalent to 250 mg of azithromycin.
ZITHROMAX® tablets are engraved with "PFIZER" on one side and "306" on the other. These are packaged in bottles and blister cards of 6 tablets (Z-PAKS®) as follows:

Bottles of 30	NDC 0069-3060-30
Boxes of 3 (Z-PAKS® of 6)	NDC 0069-3060-75
Unit Dose package of 50	NDC 0069-3060-86

ZITHROMAX® tablets should be stored between 15° to 30°C (59° to 86°F).

ZITHROMAX® for oral suspension after constitution contains a flavored suspension.
ZITHROMAX® for oral suspension is supplied in bottles with accompanying calibrated dropper as follows:

Azithromycin contents per bottle	NDC
300 mg	0069-3110-19
600 mg	0069-3120-19
900 mg	0069-3130-19
1200 mg	0069-3140-19

Storage: Store dry powder below 30°C (86°F). Store constituted suspension between 5° to 30°C (41° to 86°F) and discard when full dosing is completed.

CLINICAL STUDIES IN PEDIATRIC PATIENTS
(See INDICATIONS AND USAGE and Pediatric Use.)

From the perspective of evaluating pediatric clinical trials, Days 11-14 (6-9 days after completion of the five-day regimen) were considered on-therapy evaluations because of the extended half-life of azithromycin. Day 11-14 data are provided for clinical guidance. Day 30 evaluations were considered the primary test of cure endpoint.

Acute Otitis Media

Efficacy Protocol 1

In a double-blind, controlled clinical study of acute otitis media performed in the United States, azithromycin (10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5) was compared to an antimicrobial/beta-lactamase inhibitor. In this study, very strict evaluability criteria were used to determine clinical response and safety results were obtained. For the 553 patients who were evaluated for clinical efficacy, the clinical success rate (i.e., cure plus improvement) at the Day 11 visit was 88% for azithromycin and 88% for the control agent. For the 521 patients who were evaluated at the Day 30 visit, the clinical success rate was 73% for azithromycin and 71% for the control agent.

In the safety analysis of the above study, the incidence of adverse events, primarily gastrointestinal, in all patients treated was 9% with azithromycin and 31% with the control agent. The most common side effects were diarrhea/loose stools (4% azithromycin vs. 20% control), vomiting (2% azithromycin vs. 7% control), and abdominal pain (2% azithromycin vs. 5% control).

Efficacy Protocol 2
In a noncomparative clinical and microbiologic trial performed in the United States, where significant rates of beta-lactamase producing organisms (35%) were found, 131 patients were evaluable for clinical efficacy. The combined clinical success rate (i.e., cure and improvement) at the Day 11 visit was 84% for azithromycin. For the 122 patients who were evaluated at the Day 30 visit, the clinical success rate was 70% for azithromycin.

Microbiologic determinations were made at the pre-treatment visit. Microbiology was not reassessed at later visits. The following presumptive bacterial/clinical cure outcomes (i.e., clinical success) were obtained from the evaluable group:

Bacteriologic Eradication:

	Day 11 Azithromycin	Day 30 Azithromycin
S. pneumoniae	61/74 (82%)	40/56 (71%)
H. influenzae	43/54 (80%)	30/47 (64%)
M. catarrhalis	28/35 (80%)	19/26 (73%)
S. pyogenes	11/11 (100%)	7/7
Overall	177/217 (82%)	97/137 (73%)

In the safety analysis of this study, the incidence of adverse events, primarily gastrointestinal, in all patients treated was 9%. The most common side effect was diarrhea (4%).

Efficacy Protocol 3
In another controlled comparative clinical and microbiologic study of otitis media performed in the United States, azithromycin was compared to an antimicrobial/beta-lactamase inhibitor. This study utilized two of the same investigators as Efficacy Protocol 2 (above), and these two investigators enrolled 90% of the patients in Efficacy Protocol 3. For this reason, Efficacy Protocol 3 was not considered to be an independent study. Significant rates of beta-lactamase producing organisms (20%) were found. Ninety-two (92) patients were evaluable for clinical and microbiologic efficacy. The combined clinical success rate (i.e., cure and improvement) of those patients with a baseline pathogen at the Day 11 visit was 88% for azithromycin vs. 100% for control; at the Day 30 visit, the clinical success rate was 82% for azithromycin vs. 80% for control.

Microbiologic determinations were made at the pre-treatment visit. Microbiology was not reassessed at later visits. At the Day 11 and Day 30 visits, the following presumptive bacterial/clinical cure outcomes (i.e., clinical success) were obtained from the evaluable group:

Bacteriologic Eradication:

	Day 11		Day 30	
	Azithromycin	Control	Azithromycin	Control
S. pneumoniae	25/29 (86%)	26/26 (100%)	22/28 (79%)	18/22 (82%)
H. influenzae	9/11 (82%)	9/9	8/10 (80%)	6/8
M. catarrhalis	7/7	5/5	5/5	2/3
S. pyogenes	2/2	5/5	2/2	4/4
Overall	43/49 (88%)	45/45 (100%)	37/45 (82%)	30/37 (81%)

In the safety analysis of the above study, the incidence of adverse events, primarily gastrointestinal, in all patients treated was 4% with azithromycin and 31% with the control agent. The most common side effect was diarrhea/loose stools (2% azithromycin vs. 29% control).

Pharyngitis/Tonsillitis

In 3 double-blind controlled studies, conducted in the United States, azithromycin (12 mg/kg once a day for 5 days) was compared to penicillin V (250 mg three times a day for 10 days) in the treatment of pharyngitis due to documented Group A β-hemolytic streptococci (GABHS or *S. pyogenes*). Azithromycin was clinically and microbiologically statistically superior to penicillin at Day 14 and Day 30 with the following clinical success (i.e., cure and improvement) and bacteriologic efficacy rates (for the combined evaluable patient with documented GABHS):

Three U.S. Streptococcal Pharyngitis Studies
Azithromycin vs. Penicillin V
EFFICACY RESULTS

	Day 14	Day 30
Bacteriologic Eradication:		
Azithromycin	323/340 (95%)	255/330 (77%)
Penicillin V	242/332 (73%)	206/325 (63%)
Clinical Success (Cure plus improvement):		
Azithromycin	336/343 (98%)	310/330 (94%)
Penicillin V	284/338 (84%)	241/325 (74%)

Approximately 1% of azithromycin-susceptible *S. pyogenes* isolates were resistant to azithromycin following therapy.

The incidence of adverse events, primarily gastrointestinal, in all patients treated was 18% on azithromycin and 13% on penicillin. The most common side effects were diarrhea/loose stools (6% azithromycin vs. 2% penicillin), vomiting (6% azithromycin vs. 4% penicillin), and abdominal pain (3% azithromycin vs. 1% penicillin).

ANIMAL TOXICOLOGY

Phospholipidosis (intracellular phospholipid accumulation) has been observed in some tissues of mice, rats, and dogs given multiple doses of azithromycin. It has been demonstrated in numerous organ systems (e.g., eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and pancreas) in dogs treated with azithromycin at doses which, expressed on a mg/kg basis, are only 2 times greater than the recommended adult human dose and in rats at doses comparable to the recommended adult human dose. This effect has been reversible after cessation of azithromycin treatment. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs given daily doses of azithromycin ranging from 10 days to 30 days. Based on the pharmacokinetic data, phospholipidosis has been seen in the rat (30 mg/kg dose) at observed C_{max} value of 1.3 μg/mL (6 times greater than the observed C_{max} of 0.216 μg/mL at the pediatric dose of 10 mg/kg). Similarly, it has been shown in the dog (10 mg/kg dose) at observed C_{max} value of 1.5 μg/mL (7 times greater than the observed same C_{max} and drug dose in the studied pediatric population). On mg/m^2 basis, 30 mg/kg dose in the rat (135 mg/m^2) and 10 mg/kg dose in the dog (79 mg/m^2) are approximately 0.4 and 0.6 times, respectively, the recommended dose in the pediatric patients with an average body weight of 25 kg. This effect, similar to that seen in the adult animals, is reversible after cessation of azithromycin treatment. The significance of these findings for animals and for humans is unknown.

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1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically–Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December 1993.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests–Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.

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